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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/694,385	10/27/2003	Brian J. Stockman	6283.N DV1	5758

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EXAMINER	
SHIBUYA, MARK LANCE	
ART UNIT	**PAPER NUMBER**
1639	
MAIL DATE	**DELIVERY MODE**
07/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/694,385	STOCKMAN ET AL.	
	Examiner	Art Unit	
	Mark L. Shibuya, Ph.D.	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-20,23-26 and 28-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-20,23-26 and 28-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/28/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Application No. 10/694,385, (20040086948 A1): Claims 18-20, 23-26 and 28-30 are pending and examined.

Priority

2. This application, 10/694,385, filed 10/27/2003, states that it is a Divisional of 09/677,107; filed 9/29/2000; which claims benefit of 60/156,816, filed 9/29/1999; 60/161,682, filed 10/26/1999; and 60/192,685, filed 3/28/2000.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 3/28/07, was filed after the mailing date of the final Office action, mailed 12/18/2006. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Specification

4. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

The specification as filed does not appear to recite the limitation of the method of claim 18, "wherein the ratio of target molecule to each test compound in each sample reservoir is about 1:1".

Maintained Claim Rejections - 35 USC § 103

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 18-20, 23-26 and 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Hajduk et al.**, J. Am Chem. Soc. 1997, 119, pp. 12257-12261 (IDS entered 3/1/2004); and in view of **Keifer**, Drugs of the Future 1998, Vol. 23, No. 3, pp. 301-317 (IDS entered 3/1/2004).

This rejection is maintained for the reasons of record as set forth in the previous Office action. The rejection is copied below for the convenience of the reader.

The claims are drawn to a method of identifying a compound that binds to a target molecule, the method comprising: providing a plurality of mixtures of test compounds, each mixture being in a sample reservoir; introducing a target molecule into each of the sample reservoirs to provide a plurality of test samples; providing a nuclear magnetic resonance spectrometer equipped with a flow-injection probe; transferring each test sample from the sample reservoir into the flow-injection probe; collecting a relaxation-edited nuclear magnetic resonance spectrum on each test sample in each sample reservoir; and comparing the spectra of each test sample to the spectra taken under the same conditions in the absence of the target molecule to identify test compounds that bind to the target molecule; wherein the concentration of target molecule and each test compound in each sample reservoir is no greater than about 100 μM; and variations thereof.

Hajduk et al., J. Am Chem. Soc. 1997, 119, pp. 12257-12261, throughout the publication and abstract, disclose one-dimensional ^{1}H NMR techniques for screening libraries of compounds for binding to a macromolecule that is a protein, particularly the FK506 binding protein, ("FKBP"), by relaxation-edited detection of ligand binding; which reads on the instantly claimed method of identifying a compound that binds to a target molecule, the method comprising: providing a plurality of mixtures of test compounds, each mixture being in a sample reservoir; introducing a target molecule into each of the sample reservoirs to provide a plurality of test samples; and collecting a relaxation-edited nuclear magnetic resonance spectrum, as in *claims 18, 23, 24, 30.*

Hajduk et al., at p. 12258, para 2-p. 12259, para 2, teach relaxation-edited 1-dimension NMR detection of ligand binding to mixtures comprising a library of nine compounds containing 2-phenylimidazole, which binds to FKBP with an affinity of 200 μM, (and which absent evidence to the contrary, reads on a dissociation constant of a test compound that binds to the target molecule of at least about 100 μM, as in *claim 29*) and eight compounds that do not bind to the protein, (and wherein these compounds read on test compounds having molecular weights no greater than about 350 grams/mole, as in *claims 22, 25, 26*). Hajduk teach obtaining a relaxation-edited spectrum of the test compounds in the absence of FKBP, then obtaining relaxation-edited spectra of FKBP alone and of the test compounds in the presence of FKBP and subtraction to produce a spectrum (Figure 2B) and to identify, from the difference spectrum (Figure 2c), compounds that bind to FKBP; which reads on collecting a relaxation-edited nuclear magnetic resonance spectrum on each test sample in each sample reservoir; and comparing the spectra of each test sample to the spectra taken under the same conditions in the absence of the target molecule to identify test compounds that bind to the target molecule, as in *claim 18*.

Hajduk et al., at p. 12260, para 2-3, teach samples containing, e.g., 50 μM FKBP protein and 50 μM of each ligand, (which reads on the concentration of the target molecule and each test compound in the sample reservoir being no greater than about 50 μM, as in *claim 28*) or 100 μM stromelysin and 100 μM of each ligand, in a 95% D_2O buffered solution, (wherein the particular compounds taught have, absent evidence to the contrary, solubility in deuterated water of at least about 1mM at room temperature, as in *claim 21*; and wherein the ratio of target molecule to each test compound in the sample reservoir is about 1:1, as in *claim 27*); which reads on the claimed method wherein the concentration of target molecule and each test compound in each sample reservoir is no greater than about 100 μM, as in *claim 18*.

Hajduk et al., does not disclose methods for identifying compounds comprising providing a nuclear magnetic resonance spectrometer equipped with a flow-injection probe; and transferring each test sample from the sample reservoir into the flow-injection probe.

Keifer, Drugs of the Future 1998, Vol. 23, No. 3, pp. 301-317, throughout the publication, and especially at p. 308, para 5-p. 313, para 3, teaches probes specifically designed to handle small-volumes (less than 40 microliters), and particularly at p. 311, para 5-p. 312, para 1, teach flow injection NMR by transferring an aliquot of sample from a microtiter plate (also, Keifer, at p. 310, para 2, teaches microtiter plate-based NMR that contemplates 96-well microtiter plates; and as in *claims 19, 20*); which reads on providing a nuclear magnetic resonance spectrometer equipped with a flow-injection probe; and transferring each test sample from the sample reservoir into the flow-injection probe, as in *claim 18*.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have made and used methods for identifying compounds comprising providing a nuclear magnetic resonance spectrometer equipped with a flow-injection probe; and transferring each test sample from the sample reservoir into the flow-injection probe; and to use multiwell and 96-well microtiter plates in such methods.

One of ordinary skill in the art would have been motivated to make and use methods for identifying compounds comprising providing a nuclear magnetic resonance spectrometer equipped with a flow-injection probe; and transferring each test sample from the sample reservoir into the flow-injection probe, because Kiefer teaches transferring test samples from microtiter plates by flow-injection probe to for NMR analysis, is desirable in order to acquire high-quality NMR spectra in a rapid and automated fashion (e.g., Kiefer at p. 310, para 2, pp. 312-313, bridging paragraph), and particularly, to screen combinatorial chemistry compounds or mixtures of compounds in order to speed up the entire drug discovery process (e.g., Kiefer at p. 301, para 1).

One of ordinary skill in the art would have had a reasonable expectation of success in using methods comprising providing a nuclear magnetic resonance spectrometer equipped with a flow-injection probe; and transferring each test sample from the sample reservoir into the flow-injection probe, because Kiefer teaches such flow-injection probes were commercially available; (Kiefer at p. 308, para 3, citing the "Nanoprobe" from Varian).

Response to Arguments, 12/18/2006

Applicant has amended the claims. Applicant appears to argue that there is no motivation to combine the cited prior art references, save improper hindsight reasoning. Applicant states:

> Although Hajduk et al. may disclose specific test compounds having the desired solubility, and the desired concentrations of target molecule and test compounds, there is no teaching or suggestion that these are important features that contribute to the success of Applicants' method. Recognition of these as important features to utilize in the system of Keifer does not come absent hindsight. Even then, this recognition only occurs when one uses the information provided by Applicants' application, which is inappropriate.

Reply at p. 8.

Applicant's arguments, entered 8/31/2006, have been fully considered but they are not persuasive.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). However, the examiner respectfully submits that the traversal against hindsight reasoning is inapposite, in regard to the instant rejection. The secondary reference of Keifer is referenced for the teaching of transferring each test sample from the sample reservoir into the flow-injection probe; *not* because the primary reference of Hajduk et al., *per se*, does not disclose or suggest the compounds of the ligand library.

Furthermore, the primary reference of Hajduk et al., appears to disclose compounds of a ligand library, wherein the compound possess the properties as specified in the claims. The applicant does not argue otherwise or present objective evidence to the contrary. As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith. *See*, *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972).

Therefore, the examiner respectfully submits that the claimed invention is *prima facie* obvious over the prior art references cited in the instant rejection.

Response to Arguments

Applicant argues that the combination of elements and the advantages they provide are not taught, suggested, or appreciated by either of the references of Hajduk et al., or Keifer or the combination, thereof.

Applicant's arguments, entered 4/11/2007, have been fully considered but they are not persuasive.

In response to applicant's argument that the combination of elements and the advantages they provide are not taught, suggested, or appreciated by either of the references of Hajduk et al., or Keifer or the combination, thereof, the fact that applicant has recognized another advantage which would flow naturally from following the

suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

The primary reference of Hajduk et al., discloses compounds of a ligand library, wherein the compound possess the properties as specified in the claims. Keifer teaches transferring each test sample from the sample reservoir into the flow-injection probe. The examiner respectfully submits that the elements of the claims were familiar in the art, the methods for combining the elements was familiar in the art, and the results of that combination would be predictable, absent evidence to the contrary.

Conclusion

7. Claims 18-20, 23-26 and 28-30 are rejected.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Shibuya, Ph.D. whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Doug Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark L. Shibuya, Ph.D.
Primary Examiner
Art Unit 1639